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Leukemia & Lymphoma

JOSEPH H. BURCHENAL
HENRY D. DIAMOND

THE YEAR BOOK PUBLISHERS • INC.
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Disease-a-Month Series

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Leukemia & Lymphoma

JOSEPH H. BURCHENAL
HENRY D. DIAMOND

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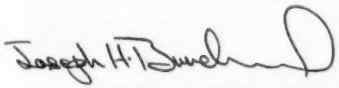

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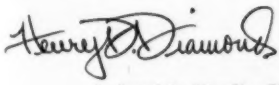

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THE LEUKEMIAS

by JOSEPH H. BURCHENAL

LEUKEMIA is a generalized neoplastic disease, primarily involving the blood-forming organs, characterized by uncontrolled production of abnormal leukocytes or their precursors and eventually by widespread infiltration of almost all tissues.

The malignant lymphomas are tumors which arise in the lymphoreticulo-endothelial structures of the body. In this discussion, Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma comprise those diseases which are classified as malignant lymphomas.

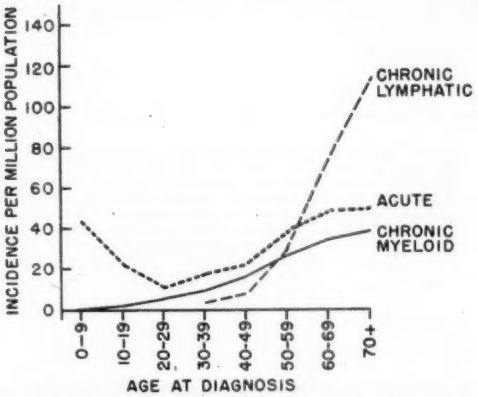


FIG. 1.—Age-adjusted incidence of leukemia in the borough of Brooklyn, 1943 to 1952. Adapted from MacMahon, B., and Clark, D., Blood 11:871, 1956.

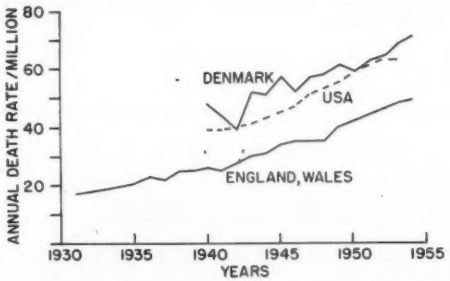


FIG. 2.—Increasing incidence of leukemia.

It has been estimated by Cameron (1) that there were 25,000 new cases of lymphoma and leukemia in the United States in 1955. Reports from the National Office of Vital Statistics (2) show that in 1953 these diseases contributed 7.6% of all cancer deaths in men and 5.4% in women. These mortality statistics show that leukemia causes 4.8% of cancer deaths in men as against 3.8% in women; and that lymphomas caused 2.8% in men versus 1.6% in women.

The Connecticut State Department of Health (3) reported

that during the 17-year period 1935-51 in the state of Connecticut leukemia and lymphomas together accounted for 9.7% of the microscopically confirmed types of cancer. The 1,661 cases of microscopically proved malignant lymphomas comprised 5.4% of the microscopically confirmed cancer cases in the state.

INCIDENCE

Studies by the Metropolitan Life Insurance Company of their industrial policyholders show that leukemia accounts for approximately one half of all cancer deaths in the 0-15 age group, one third of all cancer deaths in the 15-19 group, approximately 10% in the 25-34 group and 3% in the 45-74 group (4).

MacMahon and Clark (5) found an incidence of leukemia in the borough of Brooklyn of 64.4 per million per annum (Fig. 1) with an incidence of 71.3 and 57.7 for white males and females and of 46.5 and 30.6 for Negro males and females, respectively. Their results were based on a study of hospital records and death certificates dated between 1943 and 1952 on a series of 1,709 patients. The white-Negro difference was decreased but not eliminated by standardization to allow for differences in the age distributions of the two populations.

According to Shimkin (6), the general incidence of leukemia in the United States has gone up from approximately 40 per million per year in 1943 to 60 per million per year in 1951. Similar increases have been noted in England and Wales of from 17 per million per year in 1931 to 49 per million per year in 1954, and in Denmark from 48 in 1940 to 71 in 1954 (Fig. 2) (7, 8). Among policyholders of the Metropolitan Life Insurance Company the annual death rate per million from leukemia rose from 18 in 1930 to 47 in 1951 (4). Although it is probable that better diagnosis and better methods of reporting play a role, most investigators feel that this represents a true increase in the incidence of leukemia.

ETIOLOGY

Many investigators, particularly Furth (9, 10), Upton (11), Kirschbaum (12, 13), Kaplan (14) and Law (15, 16) who studied leukemia in mice, have demonstrated that the incidence of this disease can be increased markedly in some strains by radiation and in others by painting the animals at frequent intervals with methylcholanthrene.

Little is known about the etiology of leukemia in man, but studies such as those of the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki (17-22) have shown that massive doses of total body irradiation increase the incidence of leukemia as much as 20 to 100 times. Court Brown *et al.* (7, 8) have also reported a definite increase in the incidence of leukemia in patients with ankylosing spondylitis treated with irradiation over the spine, and in this series the incidence of leukemia seems to be proportional to the amount of irradiation received. The report that leukemia is 9 times more common among radiologists than among physicians not chronically exposed to radiation would seem to indicate that small doses of radiation over a long period may also predispose to leukemia (23, 24, 25). The data of Stewart *et al.* (26) suggest that the ionizing radiation rendered by x-ray studies of the abdomen of the pregnant woman may predispose to the later development of leukemia in the child.

The correlation between chronic benzol intoxication and the incidence of leukemia as reported by many investigators has been reviewed by Hueper (27). Although opportunities for such intensive study as with radiation have not existed to date with this agent, there seems to be strong evidence that benzol intoxication predisposes to leukemia, particularly of the granulocytic type.

Since the discovery by Ellermann and Bang (28) that one type of fowl leukemia could be transmitted by cell-free filtrates, viral etiology of many types of fowl leukemia has been confirmed by many investigators (29-34), and the more recent studies by Gross (35-37), Schwartz (38), Woolley (39), Furth (40) and Friend (41) would seem to indicate that certain of the experimentally induced leukemias in mice also have viral etiology. Although viruses have not been implicated to date as etiologic agents in human leukemia, the findings of Schwartz *et al.* (42) that cell-free filtrates of human leukemic brain had an accelerating effect on the appearance of leukemia in the high leukemia AK strain of mice suggest that with refinements of technic, it may be possible to demonstrate a virus in human leukemia.

CLASSIFICATION

There are many different classifications of leukemic cells, but a simple classification would name the type of leukemia for the predominant cell involved, with each of the cell lines subdivided

into the acute and chronic varieties, depending on the immaturity of the cells involved. Thus it is possible to have acute and chronic varieties of leukemia from overgrowth of cells of the granulocytic series, the lymphocytic series or the monocytic series and also occasionally the erythroid, megakaryocytic and plasma cell series.

PHYSIOLOGY

Since in leukemia the basic lesion is a replacement of the normal elements of the bone marrow by immature neoplastic cells derived from the blood-forming tissues, the symptoms of the disease can be divided roughly into 4 categories, according to whether they are caused by infiltration of essential organs by abnormal neoplastic white cells or by interference with the production of normal white cells, red cells or platelets.

In acute leukemia the neoplastic leukemic cells may infiltrate tissues to cause lymphadenopathy, splenomegaly, hepatomegaly, enlarged kidneys, skin infiltration and occasionally hypertrophy of the gums. This last manifestation is more common in acute monocytic leukemia. In children, periosteal elevation and infiltration of bones and joints is common, causing pain in the long bones and swelling of joints which may simulate rheumatic fever. Meningeal infiltration resulting in headache, increased CSF pressure and papilledema may mimic a true bacterial meningitis.

In acute leukemia, the marrow contains an abnormally high percentage of immature cells of the white cell series. It is usually hyperplastic, but occasionally, even before treatment, may be hypoplastic. In most cases there is almost complete replacement of the normal marrow elements by lymphoblasts, myeloblasts, promyelocytes or immature undifferentiated cells which are usually termed blast or stem cells. In certain early cases, however, particularly those of the subacute granulocytic variety, the percentage of blast cells may be much lower. As a result of the replacement of the normal marrow by the neoplastic white cells and consequent lack of normal maturing leukocytes in the peripheral blood, the patient is less able to combat infection. Ulceration and infection of the mouth, gums and anus are not infrequently seen, and abscesses and cellulitis from minor cuts and scratches are common. In the patient in whom antibiotics are not used, streptococcic or staphylococcic tonsillitis and pharyngitis or any of the previously mentioned infections may rapidly

progress to a bacteremia. These patients are also particularly susceptible to infection with organisms such as E. coli and Ps. aeruginosa, which are not usually particularly pathogenic in normal persons. The absence of normal erythroid activity in the marrow and probably also a decreased life span of the circulating red blood cells lead to a severe anemia, with the accompanying symptoms of pallor, easy fatigability and dyspnea on exertion. The hemic murmur which may be present because of this anemia may also cause the disease to be confused with rheumatic fever in children. The decreased megakaryocytic activity in the bone marrow and the decrease in platelets in the circulating blood lead to the signs of a hemorrhagic diathesis such as petechiae, ecchymoses, bleeding gums, hematuria and cerebral hemorrhage.

In chronic granulocytic leukemia the marrow is hyperplastic, with an abnormally high percentage of myelocytes and promyelocytes. In the peripheral blood the total leukocyte count is usually markedly elevated, with a high percentage of myeloid elements, ranging from myelocytes and metamyelocytes to mature polymorphonuclear leukocytes. Studies of the Atomic Bomb Casualty Commission (21) have shown that the presence of an increased percentage of basophils in otherwise normal peripheral blood may be the first indication of incipient leukemia.

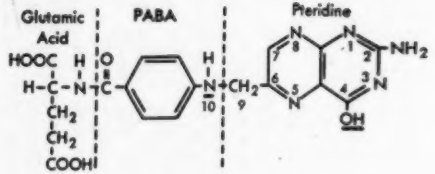
In the early stages, presumably because the peripheral blood contains an abundance of polymorphonuclear leukocytes, these patients are not so particularly susceptible to infection as are those with acute leukemia or the chronic lymphocytic form of the disease. Splenomegaly is the characteristic early physical finding in these patients and hepatomegaly usually appears somewhat later. Except in the late stages, lymphadenopathy and other tissue infiltrations do not occur, but when present these are usually bad prognostic signs. The erythroid activity is frequently depressed in the early untreated case and a mild anemia is present. In contrast to the acute leukemias or chronic lymphocytic leukemias, the platelet levels are usually normal or elevated, rather than decreased, in the chronic granulocytic form of the disease and there is less of a hemorrhagic tendency, although in some patients the first symptoms of the disease may be a tendency to bruise easily, despite the increased number of platelets.

In chronic lymphocytic leukemia, the marrow is hyperplastic and the normal elements are almost completely re-

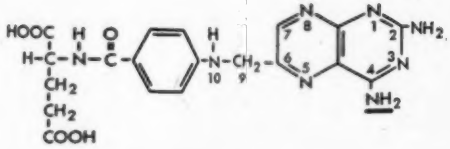
placed by small lymphocytes. In the peripheral blood, the white cell count is usually markedly elevated, with a high percentage of mature lymphocytes. The lymph nodes are usually enlarged, but splenomegaly is not so striking as in the chronic granulocytic form. Skin infiltrations and tumors may be present and low-grade infections are frequent. The erythroid activity is eventually depressed, with the consequent development of anemia, pallor and easy fatigability. In addition to this lowered production of erythroid elements, there is frequently an acquired hemolytic anemia, which markedly accentuates the anemia. The platelet levels are usually somewhat depressed, but a true bleeding diathesis may not be present until late in the disease.

TREATMENT

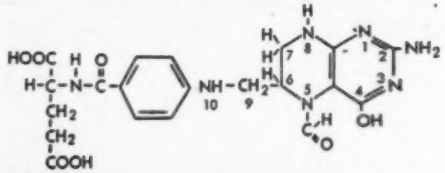
The broad aims of treatment of leukemia are (1) to return the bone marrow to its normal functioning state and (2) to cause regression and disappearance of any evidences of organ infiltration by leukemic cells. In the acute leukemias, chemotherapy is the method of choice. Irradiation for the generalized acute leukemic picture is contraindicated but the use of x-ray therapy to localized lesions such as meningeal involvement, leukemic masses pressing on the central nervous system, enlarged kidneys or localized skeletal lesions is frequently of value. The chemotherapeutic agents for acute leukemias may be divided into two general groups: (1) the antimetabolites and (2) the adrenal steroids. An antimetabolite may be defined as a compound whose chemical structure differs only slightly from some normal metabolite such as a vitamin, an amino acid or a precursor of nucleic acid (Figs. 3, 4, 5). The chemical similarity is so close that the antimetabolite is able to enter into the same enzyme systems as the normal metabolite, but once it has entered into these systems, the chemical difference is just sufficient so that the reaction can go no further and the whole enzyme system is blocked. Certain vitamins, such as folic acid and citrovorum factor, its biologically more active counterpart, are necessary for the growth and maturation of the normal erythroid and myeloid tissue of the marrow and even more necessary for the growth of the cells of some forms of acute leukemia. The first indication of the successful use of antimetabolites in the treatment of leukemia was the epoch-making report of Farber *et al.* (43), in 1948,



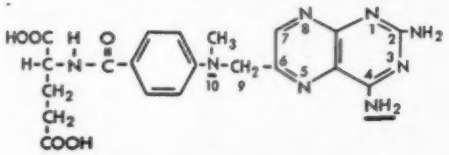
FOLIC ACID
(PTEROYLGLUTAMIC ACID-PGA)



AMINOPTERIN
(4-AMINO-PTEROYLGLUTAMIC ACID)



5-FORMYL-5,6,7,8-TETRAHYDROPTEROYLGLUTAMIC ACID
CITROVORUM FACTOR (CF)
LEUCOVORIN
FOLINIC ACID



AMETHOPTERIN (METHOTREXATE)
(4-AMINO-N^{10}-METHYLPTEROYLGLUTAMIC ACID)

FIG. 3.—Formulae of the folic acid antagonists.

of the ability of aminopterin (Fig. 3), an antagonist of folic acid, to produce remissions in children with acute leukemia.

The folic acid antagonists methotrexate (4 amino-N^{10}-methylpteroylglutamic acid) (44) and aminopterin (4-aminopteroylglutamic acid) (45) (Fig. 3) differ from folic acid mainly by the substitution of an amino group for the hydroxyl group in the 4 position of the molecule. Treatment with either of these agents causes a relative deficiency of citrovorum fac-

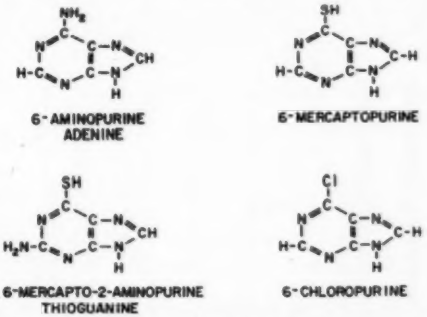


FIG. 4.—Formulae of purines and purine antagonists.

tor throughout the body which specifically damages certain types of leukemic cells. These drugs are administered orally with the usual dosage of methotrexate being 2.5-5 mg. daily in a child and 5-10 mg. daily in an adult. The dose of aminopterin for a 5-year-old child is 0.25-0.5 mg. daily and in an adult 0.5-2 mg. daily. Since there is approximately a fivefold to tenfold difference in the dosage of these drugs, it is important to differentiate between the two.

Animal studies on experimental leukemias (46, 47) and solid tumors (48) in mice have shown that methotrexate is more effective than aminopterin for the same degree of toxicity. Our experience in the clinic has tended to bear out this observation. Therefore, we recommend methotrexate in preference to aminopterin whenever a folic acid antagonist is to be given.

Both these compounds can be given by mouth, and absorption is equally rapid by the oral or intramuscular route. It has been shown that if a 5 mg. dose of methotrexate is adminis-

tered orally to a normal person on a fasting stomach, an appreciable level of the drug can be detected in the serum 15-30 minutes after injection (approximately 100 mμg./ml.) with rapid disappearance from the blood in 3-12 hours. In persons with impaired renal function, however, considerable amounts of methotrexate are found in the serum in 24-48 hours after administration (49). Particular caution should be exercised

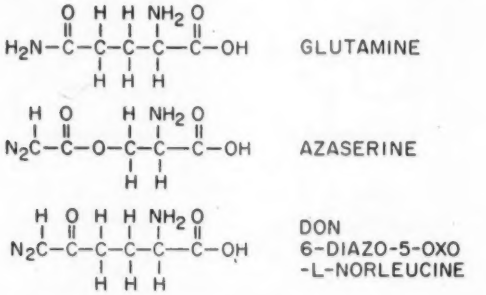


FIG. 5.—Formulae of glutamine and glutamine antagonists.

in treating such patients, since this retention leads to greatly increased toxicity.

In many children the judicious use of the folic acid antagonists may produce remissions without concomitant toxicity, but in some instances it is necessary to produce mild signs of toxicity to be sure that adequate therapy has been given. The first signs of toxicity generally noted with methotrexate are redness and ulceration of the buccal mucosa. These ulcers are usually yellowish, with a reddish areola. Loss of appetite and abdominal cramps may also occur and may be followed later by diarrhea and gastrointestinal bleeding. It would seem wise to discontinue therapy in most cases on the appearance of oral ulceration, in order to avoid disturbances further down the gastrointestinal tract. With larger doses depression of the marrow also occurs, and with severe toxicity a temporary loss of hair and cessation of beard growth may be noted.

Three to 12 weeks of constant therapy may be necessary to achieve a complete remission with the folic acid antagonists, and once such a remission is achieved the therapist has two

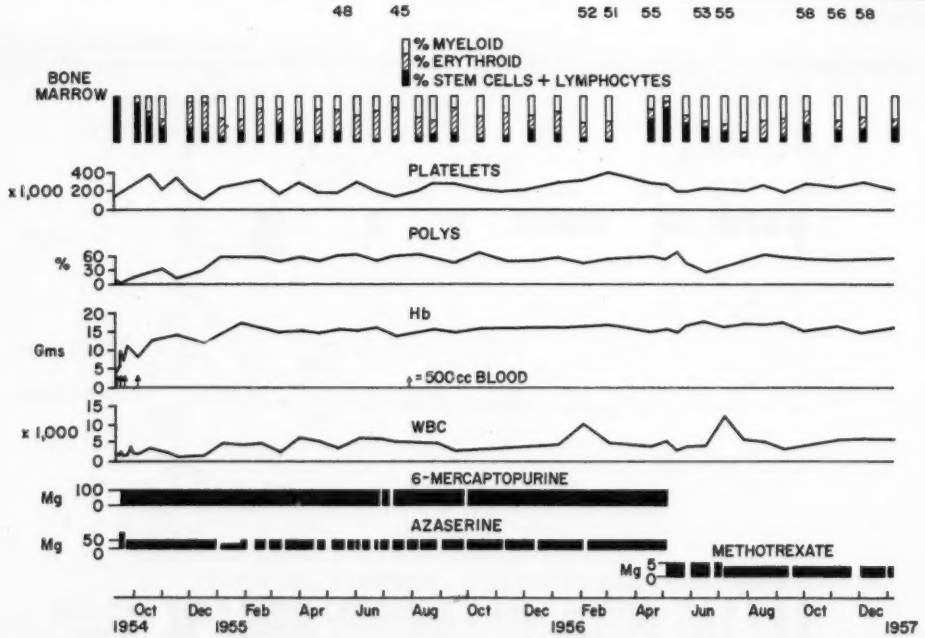


FIG. 6.—Twelve-year-old girl with acute leukemia treated with the combination of mercaptopurine and azaserine for 18 months and later with methotrexate by the maintenance therapy technic. She has now been on maintenance therapy with methotrexate for 20 months (as of January 1958).

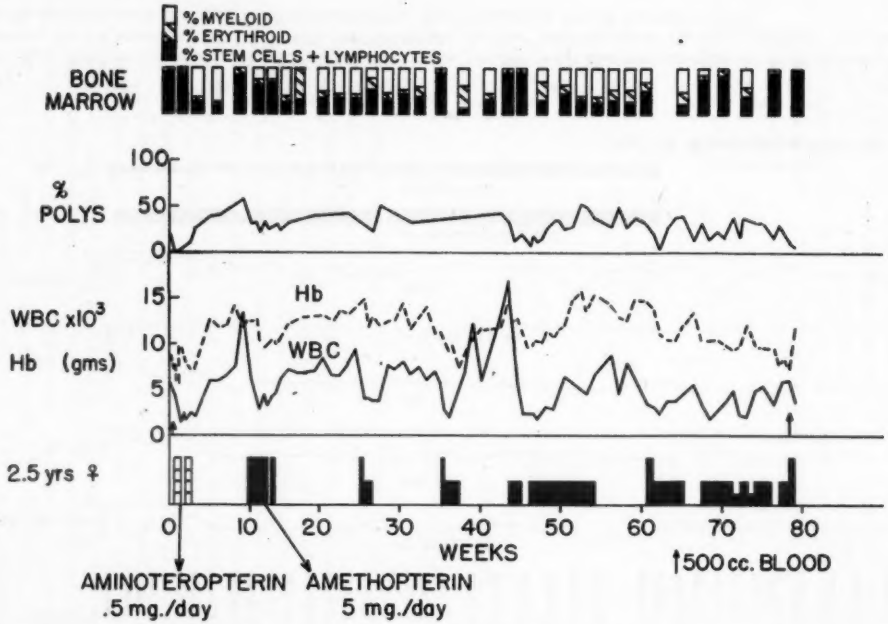


FIG. 7.—Two-and-one-half-year-old girl with acute leukemia treated with the folic acid antagonists by the intermittent dosage technic.

the intermittent dosage technic.

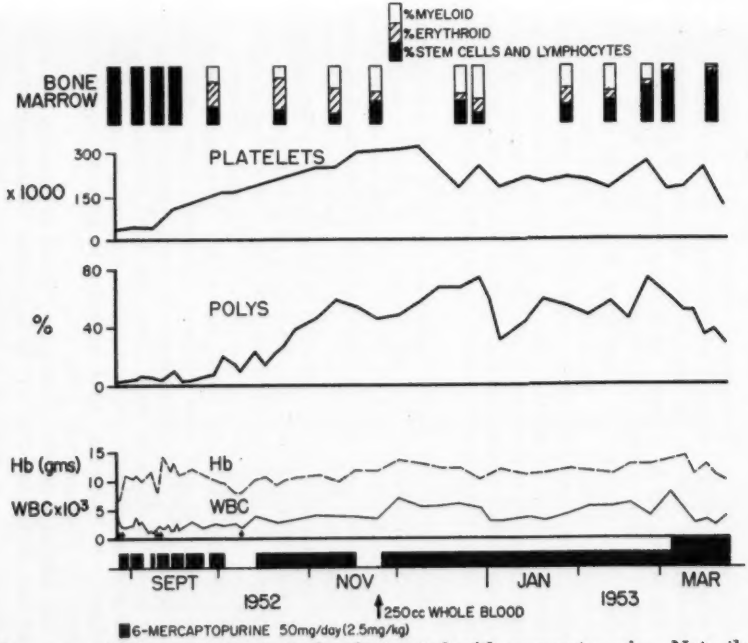


FIG. 8.—Three-year-old boy with acute leukemia treated with mercaptopurine. Note the development of resistance to 6MP by the leukemic cells in approximately 6 months.

courses open. Either he may continue maintenance therapy at approximately the same dose as was used in treatment (Fig. 6) or he may discontinue treatment and watch the patient closely for the first signs of relapse (Fig. 7). If such a course of intermittent therapy is used, the marrow should be examined preferably every 2 weeks but at least once a month in order to detect the first signs of relapse and to re-start therapy before the clinical signs and symptoms appear. With either schedule of therapy the disease may usually be controlled for from 6 months to 2 years. In his summary of the results reported at the Second Conference on the Folic Acid Antagonists (50) Farber (51) considered 68% of 425 children improved by therapy. In our initial studies with the folic acid antagonists, good remissions were achieved in 44 of 119 children and 1 of 36 adults (52). It is worth noting here that patients whose disease eventually develops resistance to methotrexate show cross-resistance to other folic acid antagonists, but not to the adrenal steroids or the purine antagonists (53, 54).

The discovery of 6-mercaptopurine (Fig. 4) as a treatment for acute leukemia was the result of a 10-year study by Hitchings, Elion *et al.* (55, 56, 57) of analogues of precursors of nucleic acid as possible chemotherapeutic agents. 6-Mercaptopurine was first shown to have an effect against Sarcoma 180 by Clarke *et al.* (58, 59) and its pharmacology was worked out by Philips *et al.* (60). The drug is generally given at a dosage of 2.5 mg. per kg. of body weight, and at that dosage in children there is little or no toxicity. In adults, however, at this or slightly higher levels, occasional symptoms of nausea and vomiting and bone marrow depression may appear. As with the folic acid antagonists, the purine antagonists require at least 3-8 weeks to exert their beneficial effects. Once a remission is achieved, it is essential to continue maintenance therapy at the same level in order to prolong remission as much as possible (54) (Fig. 8).

In addition to 6MP, two other purine antagonists are active against leukemia (Fig. 4). Thioguanine (6-mercapto-2-amino purine) (57) is given at a dosage of 2-2.5 mg./kg. daily by mouth and seems to have the same beneficial effect as 6-mercaptopurine (61). 6-Chloropurine (62), on the other hand, is given in doses of approximately 20 mg./kg. daily by mouth and at that level produces remissions at approximately the same rate as mercaptopurine in children (61) and perhaps

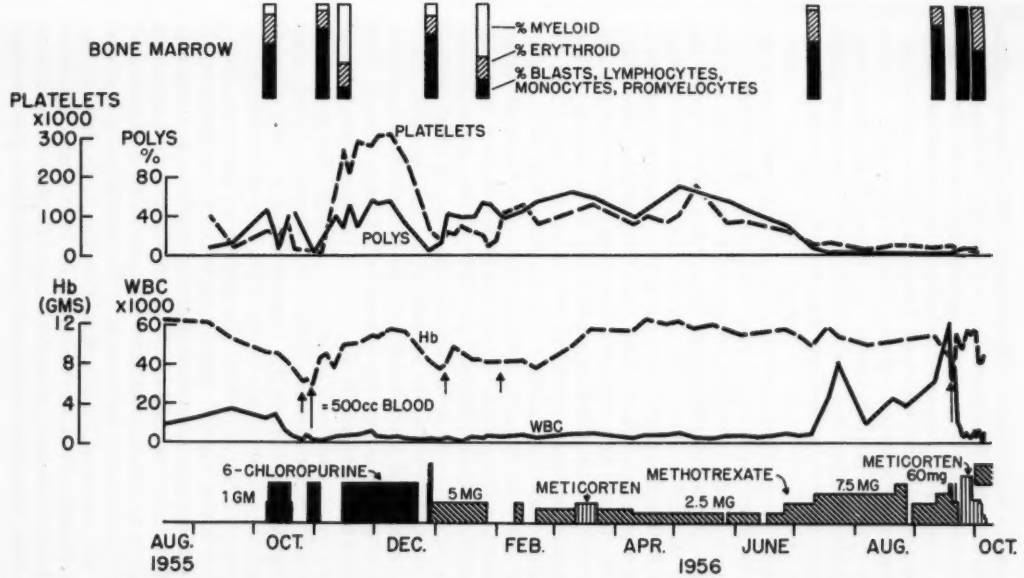


FIG. 9.—This chart shows the course of a 31-year-old woman with acute myeloblastic leukemia who responded well clinically and hematologically to 6CP. When resistant to 6CP, she responded to methotrexate. The prednisone given for 10 days during March 1956 was given at another hospital and there was no evidence of resistance to methotrexate at that time.

slightly more frequently in older adults (64) (Fig. 9). Other than this last possibility, which is at present undergoing statistical re-evaluation, it would appear that neither of these latter 2 compounds has any marked advantage over 6-mercaptopurine. As with the folic acid antagonists, the leukemic cell soon develops resistance to the purine antagonist, and resistance to 6-mercaptopurine is accompanied by cross-resistance to thioguanine and 6-chloropurine. There is no cross-resistance, however, to the folic acid antagonists or the adrenal steroids (63).

Whereas the folic acid antagonists initially are useful primarily in the treatment of acute leukemia in children, the purine antagonists are effective not only in children but also in adults, although in the adult group the responses are less common than in children (54, 64, 65). In correlation with the work of Law (66) there also appears to be some indication, from the studies of Ellison (67), that those adult patients who have been treated first with mercaptopurine and have then developed resistance to it will respond better to methotrexate than they would have been expected to respond initially (Fig. 9).

The glutamine antagonists (Fig. 5) have also been studied for their effect on leukemia. Their discovery occurred during the testing of various crude filtrates of Streptomyces for tumor-inhibitory activity by Ehrlich *et al.* (68), Bartz *et al.* (69) and Stock *et al.* (70). This yielded an agent which inhibited the growth of various solid tumors and leukemias in experimental animals, which on purification and characterization proved to be o-diazoacetyl-l serine (azaserine). Further studies of similar filtrates of an unidentified species of Streptomyces have led to the isolation, characterization and finally the synthesis of 6-Diazo-5-oxo-L-norleucine (DON), a closely related compound, by Ehrlich *et al.* (71), Dion *et al.* (72), DeWald *et al.* (73) and Westland *et al.* (74). DON was demonstrated by Clarke *et al.* (75) to inhibit the growth of Sarcoma 180 in mice at levels 1/40-1/80 those required with azaserine. This compound also has a marked inhibitory effect on transplantable leukemia in the mouse (76). Both these compounds have been shown to act as glutamine antagonists in a pigeon liver system (77, 78) and in bacteria (79) in inhibiting the conversion of formyl glycine amide ribotide to formyl glycine amidine ribotide (the incorporation of N into the 3-position of the purine skeleton). Murphy *et al.* (80, 81) have demonstrated that azaserine causes fetal resorption and develop-

mental anomalies in surviving rat fetuses after a single dose of 2.5 mg./kg. to the mother on about the 10th day of gestation (1/40 the maternal LD_{50} dose) (82). These data would appear to demonstrate striking tissue specificity.

In the patient the maximal tolerated dose of azaserine when given alone by either the intravenous or oral route is approximately 10 mg./kg. of body weight daily (83) and of DON is 0.25 mg./kg. daily (117). Given at these doses, both drugs produce redness and ulceration of the buccal mucosa, lips and tongue in approximately 1-2 weeks. These symptoms are sometimes associated with heartburn and gastrointestinal distress. Neither azaserine nor DON when given alone to children with acute leukemia has any practical beneficial effect, although as noted below both may be of some value in combination with 6-mercaptopurine.

Since, so far, only quantitative differences have been demonstrated between normal and leukemic cells, it is questionable whether any single agent will be adequately specific to control the disease indefinitely. Because of this, sequential blocking (84) of several different sites in a given metabolic pathway essential for the metabolism of the leukemic cell would seem to be the most rational approach to chemotherapy. Skipper (85) and Law (86) have shown an additive therapeutic effect for the combination of 6MP and methotrexate against L1210 leukemia, but Clarke (87) in Sarcoma 180 and Goldin (88) in L1210 leukemia could find no real synergistic effect without severe concomitant toxicity. Similarly, preliminary clinical trials of such combinations have not demonstrated synergistic effects against leukemia. The combination of 6MP and azaserine, or 6MP and DON, however, has been shown by Clarke *et al.* (89) to be synergistic against Sarcoma 180. Similar synergistic effects have been shown by others against some strains of mouse leukemia (76). Since mercaptopurine presumably acts to prevent the incorporation of a hypoxanthine-containing precursor into nucleic acid, and azaserine and DON prevent the amination of formylglycine amide ribotide to formylglycine amidine ribotide, a step in the de novo synthesis of the purine ring, this suggests a rationale for the use of these 2 compounds in combination, as, perhaps, sequential blocking agents in the synthesis of purine polynucleotides.

For this reason, the combination of mercaptopurine and azaserine has been studied in children with acute leukemia (63). Under treatment with the combination of equal doses of 2.5

mg./kg. daily by mouth of 6MP and azaserine, signs of toxicity, such as redness and ulceration on the tongue and buccal mucosa frequently appeared, in which case it was necessary to stop the azaserine component for 2-3 days and then resume at half dose, continuing 6MP at the full dose throughout the course. In some cases, the full dose of 2.5 mg./kg. body weight of each drug daily was continued for many months; but, as previously mentioned, in most others maintenance dosage of 1.25 mg./kg. of the azaserine component, combined with a full dose of 6MP, was all that could be tolerated (Fig. 6). Similar toxic symptoms were noted when DON was given in combination with mercaptopurine at doses of 0.25 mg./kg./day of DON. The ulcerations of the buccal mucosa did not seem to be associated with any gastrointestinal ulceration or bleeding, as with the antifolic, so that the oral toxicity, unless it was acutely uncomfortable to the patient or interfered with nutrition, was not alarming. With the DON-mercaptopurine combination, too few cases have been treated at present to have any indication whether it adds anything to mercaptopurine alone, but at least it is known that some children have been able to tolerate this combination for as long as 9 months without any ill effects.

It would appear that in children with acute leukemia the addition of azaserine to the standard therapeutic dose of mercaptopurine by mouth increased somewhat the length of remission over that achieved with mercaptopurine alone. A cooperative study is now under way with some 13 groups to determine whether the apparent advantage of this combination over 6MP alone is really significant.

The hormones, ACTH, cortisone, compound F and prednisone are all quite useful in the treatment of acute leukemia (90-92), particularly where it is essential to achieve a remission with great rapidity (63). Generally, the remissions induced with these compounds do not last as long as those achieved with the antimetabolites. ACTH is perhaps the most rapidly acting of all the compounds and is most effective when given by constant intravenous drip of 25-50 mg. daily. Cortisone, compound F or prednisone can be given orally, and of these we prefer prednisone. The average dose of this steroid for a child is approximately 50 mg. and for an adult 100 mg. daily given in divided doses. The undesirable side effects such as sodium retention and consequent edema, which are seen with most of the steroids, rarely occur with these doses of pred-

nisone. On the other hand, hypertension, mental changes and the development of Cushing facies are occasionally noted with all these compounds. Any of the above-mentioned hormones will produce a high percentage of remissions in the acute leukemias of children, from 50 to 70%, and are also moderately effective in young adults. Past the age of 30, however, the remissions are relatively rare, but in an acute emergency they should probably be used in any age group.

Plan of Therapy

We believe (63) that the antimetabolites, such as the folic acid antagonists and the purine antagonists, produce longer remissions than the steroids, but that at least 3-8 weeks are necessary for these compounds to achieve their beneficial effect. For this reason, if a patient appears to be in good enough general condition so that there will be adequate time for the antimetabolites to exert their beneficial effects, they should be used as the primary form of treatment. On the other hand, if the patient is acutely ill with a hemorrhagic diathesis and a rapidly progressing disease, and sufficient time is not available, the treatment of choice would be adrenal steroids to achieve an initial remission, followed by maintenance therapy with the antimetabolites. We feel that the steroids are of great importance in the therapy of acute leukemia but that they should be saved for the situations in which they alone are beneficial.

Results

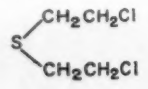
Since a high percentage of children respond to one or more of the types of chemotherapeutic agents, these responses have been reflected in increases in survival time following treatment. A survey of the literature by Tivey (118) showed that in a series of 218 relatively untreated children with acute leukemia the median survival time was 3.9 months, whereas a series of 184 consecutive children with acute leukemia treated at Memorial Center during the years 1952-1955 when the folic acid antagonists, the purine antagonists, the glutamine antagonists and the adrenal steroids were available as therapeutic tools, showed a median survival time of 12.4 months. Although the actual remissions in children to a given agent may be no longer than those achieved in adults, the percentage responding to

each agent is much higher in children than in adults. Ellison (67) has noted that the median survival time in a group of adults with acute leukemia treated at Memorial Center prior to the use of purine antagonists was 6 months. No significant difference in survival time could be demonstrated in the group of adult acute leukemics as a whole during the next 4 years, when the purine antagonists were available. Those patients, however, who had either a complete or partial remission did show an increase in the median survival time to 11 and 8 months respectively. These periods of remission were periods of well-being and in most cases patients could lead normal lives during remissions. For these reasons we feel that in addition to using all the supportive therapy indicated it is imperative to treat all patients with acute leukemia, be they children or adults, with the specific agents available.

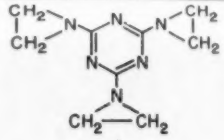
Treatment of Chronic Granulocytic Leukemia

There are many forms of therapy which are beneficial to the patient with chronic granulocytic leukemia in the early stages. Localized deep x-ray therapy over the spleen at doses of 50-100 r daily, alternating anterior and posterior ports until a total of 600 r has been given, will usually suffice to bring the count down, but in some cases it may be necessary to go higher. It is advisable to keep the white count below the 20,000 range and start therapy again as soon as the count begins to go above this level. Total body spray x-ray or the oral or intravenous administration of radioactive phosphorus can also be used. Osgood (93) in particular has reported significant increases in survival time from titrated regularly spaced small doses of radiation delivered by either of these means of total body irradiation.

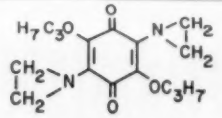
Of the chemotherapeutic agents available for the treatment of chronic granulocytic leukemia, arsenic was the first to be employed by Lissauer in 1865 (94). This form of treatment was temporarily forgotten when x-ray therapy appeared at the turn of the century, but was resurrected in 1931 by Forkner and Scott (95). The usual dose is 5 minims 3 times daily of Fowler's solution, increasing one minim daily until a total dose of 20 minims 3 times daily is given or until nausea and vomiting appear. The difficulty with this form of treatment is that it often causes such severe nausea and vomiting that it cannot



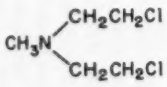
Sulfur mustard
Bis-β-chloroethyl sulfide



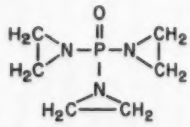
Triethylene melamine (TEM)
2,4,6-Triethylenimino-s-triazene



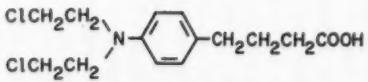
E-39
2,5-Diethyleneimino-3,6
diproproxy-1,4-benzoquinone



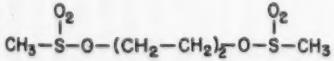
Nitrogen mustard (HN2, Mustargen)
Methyl bis-(β-chloroethyl)amine



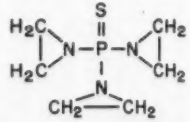
Triethylene phosphoramide
(TEPA)



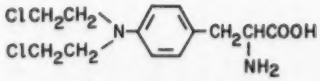
CB 1348 chloroambucil
p-di(β-chloroethyl)-
aminophenylbutyric acid



Myleran (G.T. 41)
1,4-Dimethane sulfonyl oxybutane



Triethylene thiophosphoramide
(Thio-TEPA)



CB 3025 sarcolysin
p-di(β-chloroethyl)-
aminophenylalanine

FIG. 10.—Alkylating agents.

be tolerated for a sufficient length of time to produce satisfactory results.

Another agent which has been reported to be beneficial in this form of the disease is benzol, which is administered in doses of 4 cc. daily by mouth in olive oil. This drug has been studied mostly by the Hungarian school of Koranyi (96) and Kalapos (97) and is rarely used in this country.

Urethane (ethyl carbamate) was shown by Paterson *et al.* (98) in 1946 to be effective in controlling the white count and achieving temporary remissions in this form of the disease. The usual dose is 3 Gm. daily by mouth. This regimen will generally bring the leukocyte count down to normal levels within a month. This drug, too, causes considerable nausea and vomiting in some patients and therefore has a somewhat limited value.

Most of the nitrogen mustards and other polyfunctional alkylating agents can also be used for the treatment of this disease (Fig. 10). HN2 (methyl-bis-[beta chloroethyl]amine) was the first to be used, and courses of 0.4 mg./kg. given either as a single dose, or a daily dose of 0.1 mg./kg. for 4 days intravenously will produce good remissions lasting 2-6 months (99, 100). The disadvantages are the temporary nausea and vomiting produced by the immediate injection and the fact that the dosage must be given intravenously. A related ethylenimine, triethylene melamine (TEM) has the advantage that it can be given either by mouth or intravenously, and causes much less nausea and vomiting (101). Triethylene phosphoramide (TEPA) (102, 103) and triethylene thiophosphoramide (thio-TEPA) (104) are of somewhat similar chemical configuration and have about the same value in this disease. Of the polyfunctional alkylating agents, the drug of choice at the present time appears to be Myleran®, which was shown by Haddow and Timmis (105) to be effective against experimental tumors in rats and shown by Galton (106) and other investigators (107) to be effective against chronic granulocytic leukemia. They concluded that this compound acted more specifically against the granulocytic series than the lymphocytic series and for this reason was particularly suited to chronic granulocytic leukemia. Dosage with this drug is generally initiated at 4-6 mg. daily by mouth; at this level the absorption appears to be constant, without nausea, vomiting or other undesirable side effects. At this dosage the total leukocyte count will usually return to normal within 30 days and,

following that, maintenance therapy may be continued at 2 mg. daily or 2 mg. twice weekly as appears indicated. Once a remission is achieved with this drug, some investigators discontinue therapy, but we believe that if therapy is discontinued the patient should be watched closely and treatment started again as soon as the leukocyte count shows any evidence of climbing above normal levels. Since Myleran®, in addition to affecting the granulocytic series may also depress the platelets, it is essential that platelet counts as well as total leukocyte counts be done to check progress of the disease and influence of the drug.

Although the folic acid antagonists when pushed to the point of severe toxicity will decrease leukocyte count and diminish organ infiltration, the purine antagonists are the only group of antimetabolites which have so far been shown to be of practical value in the therapy of chronic granulocytic leukemia. Most of the experience has been with 6-mercaptopurine (54) although both 6-chloropurine and thioguanine have also been shown to be effective (61). As in acute leukemia, it is given at doses of 2.5 mg./kg. body weight daily by mouth and will produce remissions in a high percentage of the cases in the early stages of the disease. Since experience has shown that most patients relapse rather rapidly within 4-6 weeks (Fig. 11) after mercaptopurine is stopped, it is advisable except in rare cases (Fig. 12) to continue maintenance therapy with this drug after a remission has been achieved. One should watch the blood counts closely, however, since after 9-24 months of therapy, drug-induced decreases in hemoglobin and in platelet levels may occasionally be seen (Fig. 13). In this case, if the compound is stopped at the first sign of such changes in hemoglobin, regeneration of the erythroid and megakaryocytic elements will occur and the anemia and thrombocytopenia will disappear.

With the many modalities of therapy available for the early stages of this disease, it would seem advisable to consider which is preferable as initial treatment. If one has good liaison with a competent radiologist and physicist, then either localized radiation over the spleen, total body spray or radiophosphorus are excellent treatment and probably at least as satisfactory as chemotherapy. If, however, such close co-operation is not available, or is difficult, chemotherapeutic agents such as Myleran® would seem to be preferable. Also, since the use of Myleran® keeps the treatment of the patient entirely in

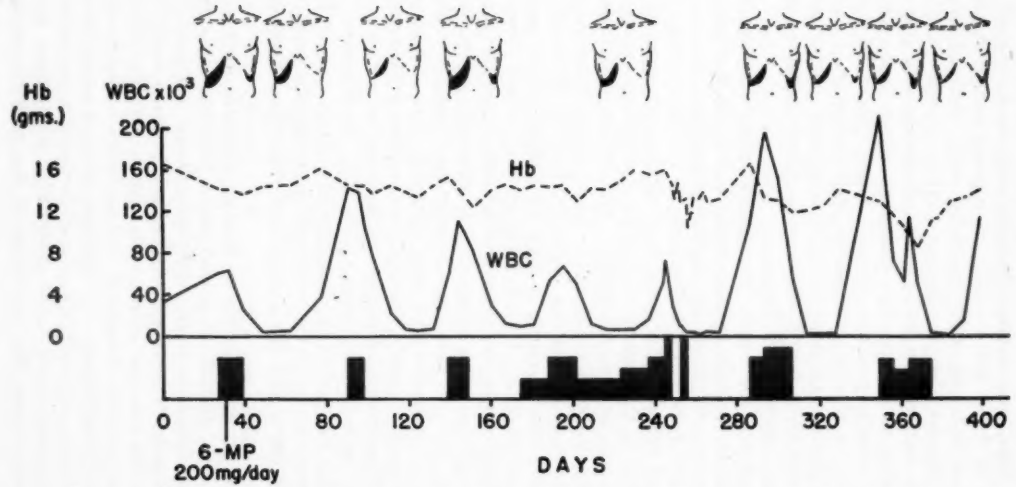


FIG. 11.—Effects of intermittent therapy with 6-mercaptopurine in chronic granulocytic leukemia.

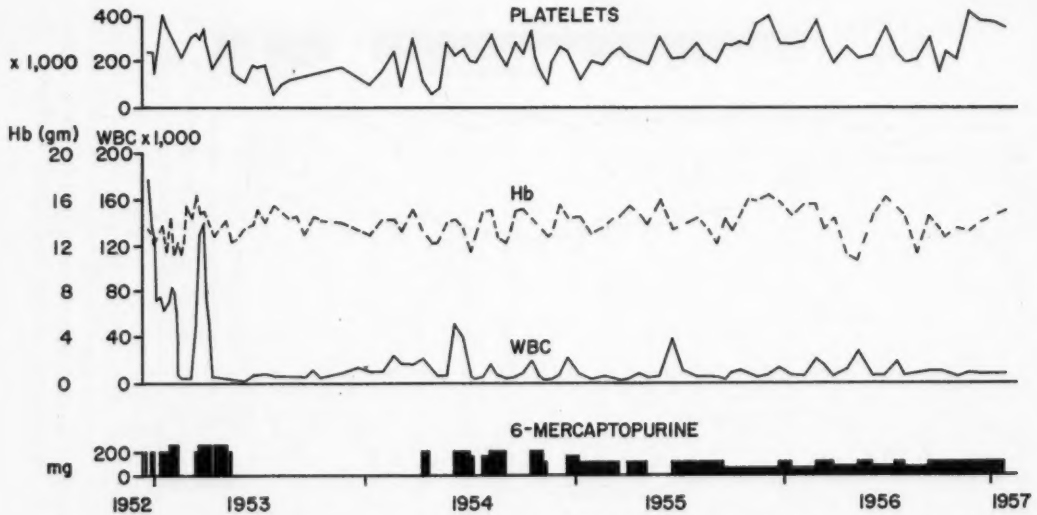


FIG. 12.—Long remission (5 years as of January 1958) in chronic granulocytic leukemia treated with 6-mercaptopurine.

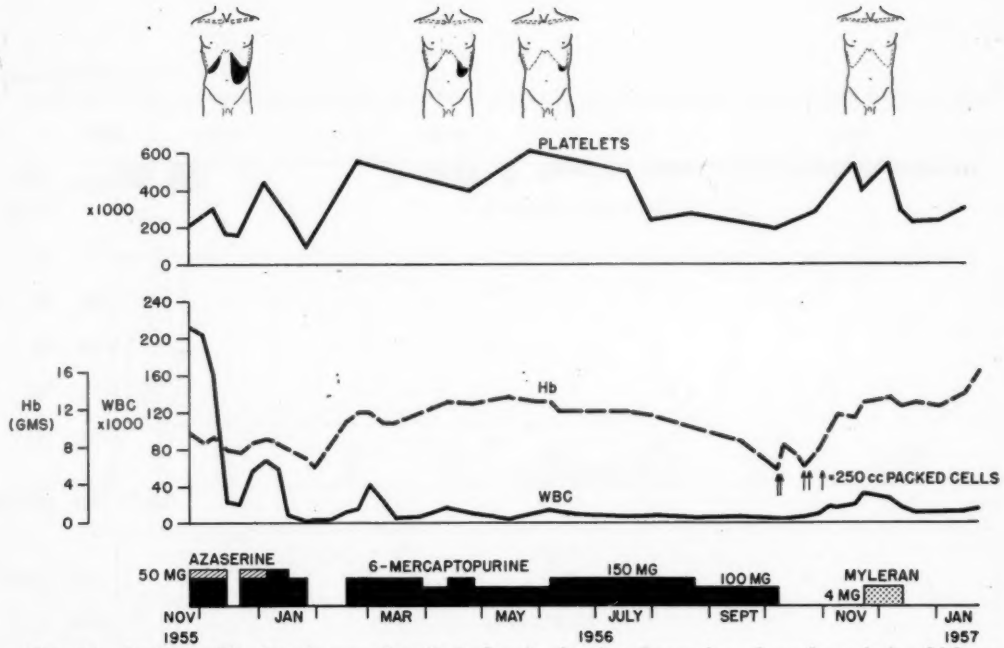


FIG. 13.—Patient with chronic granulocytic leukemia showing depression of erythropoiesis which occurred after 11 months of therapy with 6MP.

the hands of the hematologist, there are many who feel that this is a distinct advantage. Although, as mentioned above, 6-mercaptopurine will also produce excellent remissions in patients with chronic granulocytic leukemia in the early stage, the fact that it occasionally also produces remissions in the late, so-called terminal stage when other forms of therapy have failed suggests that there might be an advantage in saving this drug until late in the disease. At that time it should be used in the same dosage, or higher if necessary, and maintenance therapy should be continued when and if a remission occurs. Remissions associated with 6-mercaptopurine administration at this late stage are relatively short, compared with what might be expected with this or other agents earlier in the disease. Myleran® and 6-mercaptopurine have not been in use long enough so that adequate numbers of patients treated with these agents are available for comparing the actual survival time with similar groups treated initially with radiation. For this reason it is impossible to make a definite statement at this time as to the comparative effects on survival time of the 3 types of agents in this disease.

Treatment of Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is an extremely variable disease and may be asymptomatic, particularly in the elderly patient, for many years. It is the general consensus that treatment, other than watchful waiting, is not indicated in the patient with only an elevated white count and no lymphadenopathy, splenic or hepatic enlargement and no symptoms. When symptoms appear, however, treatment should be initiated. If the main complaints stem from localized enlargement of the nodes, x-ray therapy to these regions would seem to be the treatment of choice. If there is a high white count and generalized glandular enlargement, spray x-ray, P^{32} therapy, certain of the polyfunctional alkylating agents such as HN2, triethylene melamine (TEM) or a new and apparently better tolerated nitrogen mustard known as chlorambucil (CB-1348) may be used. Chlorambucil (p-[di-chloroethylamino]-phenylbutyric acid) was originally used by Galton *et al.* (108) for the treatment of this disease and was felt by them to be well tolerated by the oral route and to be more specific for the lymphoid tissue than for the granulocytic or the meg-

curred after 11 months of therapy with 6MP.

akaryocytic elements of the marrow. This compound has been studied in the United States by Bouroncle *et al.* (109), Hall *et al.* (110), Ultmann *et al.* (111) and Altman *et al.* (112), and excellent results in chronic lymphocytic leukemia treated at doses of 0.2 mg./kg. daily by mouth have been reported. Treatment is generally continued at this dosage until the leukocyte count begins to fall and then discontinued, or continued as maintenance therapy at a smaller dose.

In the patient who develops acquired hemolytic anemia or thrombocytopenia as part of the disease picture treatment with adrenal steroids is indicated, and in this situation prednisone would appear to be the drug of choice. Hemolytic anemias in general respond well to this, but in some cases splenectomy may be indicated. Doses of prednisone of 30-60 mg. daily in divided doses are usually sufficient, although in some cases doses as high as 100 mg. may be necessary. In so variable a disease it is difficult to assess the effect of a specific therapy on survival time. Certainly by these measures the useful and perhaps also the actual life of the patient may be prolonged.

Supportive Therapy

In addition to the specific therapy of leukemia discussed above, the concept of "total care" of the patient with leukemia as stressed by Farber (51) is particularly important. Appropriate antibiotics should be used promptly at the first signs of infection. The physician should be particularly aware of the possibility of infections with Ps. aeroginosa and also with a penicillin-4 and tetracycline-resistant strain of Micrococcus pyogenes.

When the patient is not in remission, transfusions should be given when the hemoglobin level falls below 7-8 Gm., or sooner if symptoms are bothersome. For the slowly falling hemoglobin level in the absence of evidence of bleeding, packed red cells are preferable, but in the patient with active bleeding whole blood is more satisfactory. Severe hemorrhagic manifestations can be combated temporarily by transfusions of fresh whole blood taken in a plastic system or by infusions of platelet substance (113).

In the child with acute leukemia the development of headache, papilledema and increased cell count in the spinal fluid in the absence of a positive CSF culture or other evidence of

infection suggests leukemic infiltration of the meninges. Since the levels of methotrexate (114) and mercaptopurine (115) in the cerebrospinal fluid are much lower than those encountered in the blood when these drugs are administered orally, this meningeal infiltration may occur at a time when the peripheral blood and marrow are in complete remission. Treatment until recently has been limited to x-ray therapy of the whole cranium through opposed lateral fields using 250 kv., half-value layer 2 mm. copper and 50 cm. target-skin distance. Dosage is 50 r in air for the first 2 doses, 100 r for the second 2, 150 r for the third 2, continued at the same daily dose until the symptoms subside or the CSF leukocyte count falls below 100. The usual midplane tissue dose has totaled 300-500 r in 5-10 days (116). Recent studies by Whiteside *et al.* (119) have demonstrated that intrathecal injections of methotrexate, 0.5 mg./kg. given every 5 days for a total of 3 injections will also control the leukemic involvement of the meninges. The levels of methotrexate attained by this technic are so high that this form of therapy is effective in patients whose disease in peripheral blood and marrow has developed resistance to methotrexate as well as in those whose systemic disease is still sensitive to the drug. Since the intrathecal administration of methotrexate at this level has an appreciable depressant effect on the marrow, oral therapy with the drug should be interrupted during the period of intrathecal administration.

Hyperuricemia and hyperuricosuria and kidney shutdown are potential dangers in the patient with high leukocyte count and marked tissue infiltration. It is essential in such a patient to force fluids sufficiently to maintain a daily urinary output between 1,000 and 3,000 cc. to alkalinize the urine, and to lower the leukocyte count gradually.

SUMMARY

The incidence of all types of leukemia appears to be increasing. Acute leukemia is most common in the first decade of life and in the age groups over 60 (Fig. 1). Chronic granulocytic leukemia is most common in early adult life and middle age, while chronic lymphocytic leukemia occurs most commonly in the older age groups. At the present time, irradiation appears to be the only proved etiologic factor for leukemia, and that only in the chronic granulocytic and acute forms, although benzol is strongly incriminated. Fowl and animal leu-

kemias have been demonstrated to have a viral etiology, but this has not as yet been proved for man. In leukemia it is particularly easy to follow the response to treatment, since the neoplastic cells are almost always available at the finger tip for examination. Most of the chronic leukemias and the acute leukemias in children will respond to one or another form of treatment. However, acute leukemias in adults, particularly in the older age groups, are less responsive, but they too will occasionally respond to chemotherapy. Unfortunately, in all patients with leukemia, no matter how good the original response may be, the leukemic cells eventually develop resistance to therapy. It would seem likely, however, that since such excellent remissions can be brought about even temporarily with the present forms of therapy, that conquest of this disease can eventually be achieved. Further investigation into the possible viral etiology of the disease in man, search on a broader scale for new chemotherapeutic agents, and further intensive study of the mechanisms of resistance appear to be the areas of research most likely to lead to this goal.

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THE LYMPHOMAS

by HENRY D. DIAMOND

IT IS THE AIM of this paper to present the manifold clinical expressions of the malignant lymphomas and to demonstrate the methods of management of patients with these diseases. A fundamental knowledge of the natural history of these maladies and of the scope and limitations of all available methods of treatment is essential for the clinician in his dealings with patients having malignant lymphomas. The physician accepting the responsibility for the diagnosis and treatment of these patients must be capable of understanding and organizing the relationships of all the disciplines and specialties of medicine as they refer to the individual patient. He must be ready to treat not only the cancer, but the patient as well.

PATHOGENESIS

The etiology of Hodgkin's disease is unknown. Opinion is divided as to whether infection or neoplasia is the cause. It is our belief that Hodgkin's disease is a malignant neoplasm. Lymphosarcoma and reticulum cell sarcoma are true cancers. These three diseases are cancers which originate in lymphatic or reticuloendothelial tissue by virtue of unrestricted, undirected, autonomous proliferation and growth. They are characterized by local invasiveness and destruction and the ability to spread to distant areas of the body. They may arise in a single structure (unicentric) and metastasize or occur in mul-

tiple sites simultaneously (multicentric). No tissue or organ is invulnerable to these diseases. Most often they seemingly originate in lymph nodes, yet genesis in extranodal sites is not unusual. These cancers occur more often in males than females, and they occur in all races, creeds and nationalities. Hodgkin's disease has its highest incidence in young adults, and while it may occur at all ages, it is seldom seen before the age of 6. Lymphosarcoma arises more often than Hodgkin's

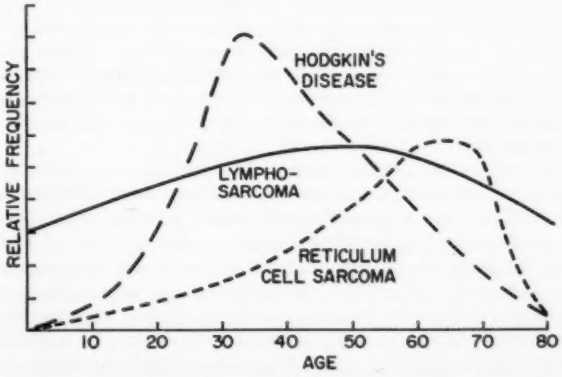

FIG. 14.—Relationship of age to incidence of malignant lymphomas.

disease in young children and is frequently then associated with an eventual appearance of an acute lymphatic leukemia. It appears with fairly regular consistency through all age ranges. Reticulum cell sarcoma develops with greater frequency as age increases (Fig. 14).

The symptoms and signs of these maladies are similar and are due mainly to the pathologic features of local invasion, early dissemination, widespread systemic involvement and the resulting pathophysiologic alterations in the host. The earliest sign is usually that of a painless, enlarged lymph node mass. This may be in lymph nodes of the neck (highest incidence), mediastinum, axilla, groin, para-aortic or retroperitoneal areas. Splenomegaly or hepatomegaly may be the initial manifestation. Solitary involvement of an intraoral structure such as the

gum, tonsil or tongue may occur (1). Primary origin in the skin, though less usual than in a lymph node, is not infrequent, especially by lymphosarcoma and reticulum cell sarcoma. Early in these diseases there are usually no constitutional symptoms, but as they progress or as metastases appear, fever, weight loss, asthenia and anemia become evident.

The diagnosis of malignant lymphoma, be it Hodgkin's disease, lymphosarcoma or reticulum cell sarcoma, is a pathologic one depending on the study of the histology of suitable biopsy material. It is the physician's responsibility, however, to consider malignant lymphoma in his differential diagnosis in any patient who manifests cryptogenic fever with or without adenopathy, or in conjunction with hepatosplenomegaly; and it is incumbent on him to recommend biopsy and pathologic examination of appropriate tissue so that a pathologic diagnosis can be established.

The choice of suitable material for biopsy as well as the manner of the biopsy, is important. Whenever possible, lymph nodes other than inguinal nodes should be chosen for biopsy. The architecture of inguinal lymph nodes may be altered so much by previous or repeated infection in the lower extremities, perineum, genitalia and buttocks as to render almost impossible correct diagnosis even by a competent pathologist. Whenever feasible, an *entire* lymph node should be excised for pathologic examination. Satellite nodes about the main nidus of nodal disease should not be elected for removal and pathologic examination unless it is technically unwise to excise and examine the prime mass of diseased lymph nodes.

Excisional surgical biopsy is the preferred method of removal of appropriate tissue. When this is not possible or is unwise for technical reasons, incisional wedge biopsy should be carried out. When the tongue, tonsil or thyroid gland is involved, such sites may be biopsied successfully by reaming or punch technics. Aspiration biopsy, though frequently definitive enough to make the pathologic diagnosis of malignant lymphoma, will seldom suffice to allow the pathologist to diagnose the exact type of malignant lymphoma. The limitations of aspiration biopsy may reflect the pathologist's limited training and consequent reluctance to interpret such material; the technic is limited inherently by its failure to preserve tissue architecture. Occasionally, surgical exploration and biopsy may be indicated as the only method of establishing the diagnosis.

PATHOLOGY

Hodgkin's Disease

There are 3 varieties of this disease recognized histologically by the competent pathologist: Hodgkin's paragranuloma, Hodgkin's granuloma and Hodgkin's sarcoma (2).

Hodgkin's paragranuloma.—This type essentially involves lymph nodes. Microscopically the normal architecture may or may not be intact, and the follicles may show varying degrees of preservation or disruption. The diagnosis must be based on the presence of Sternberg-Reed cells, which may be sparse or numerous, but the predominant cell seen is the adult lymphocyte. When the lymph follicles are obliterated and diffuse nodal infiltration by such lymphocytes is great, an erroneous diagnosis of lymphosarcoma (lymphocytoma) may be made. Plasma cells are usually seen, and some eosinophils may be present. Incomplete tuberculoid granulomas resembling Boeck's sarcoid may be observed. There is no necrosis, polymorphonuclear infiltration, marked eosinophilia or fibrosis (2).

Hodgkin's granuloma.—This is the classic form of Hodgkin's disease and may be nodal or extranodal. There is usually complete loss of normal architecture in the node. Extension of the process into the capsule may occur. The granuloma is characterized by the presence of Sternberg-Reed cells and its pleomorphism. Lymphocytes are numerous, plasma cells are consistently present and eosinophils are almost always present to some degree. Necrosis and fibrosis are evident. Abortive focal tubercle formations resembling Boeck's sarcoid may be present (2).

Hodgkin's sarcoma.—This form may be nodal or extranodal and is invasive and destructive. It is characterized by cells which are larger than normal lymphocytes. Sternberg-Reed cells, though sparse, are seen. There are scattered lymphocytes and reticulum cells. Necrosis is evident. Normal architecture is lost, and the perinodal fat and areolar tissue are frequently invaded. Mitotic activity of the Sternberg-Reed cells is high (2).

It must be remembered that in a single patient one node may show Hodgkin's paragranuloma while another will demonstrate Hodgkin's granuloma. In fact, serial sections of a

single node may occasionally reveal Hodgkin's paragranuloma, granuloma and sarcoma.

Lymphosarcoma

There are several varieties of lymphosarcoma, both clinical and pathologic.

Giant follicle lymphoma.—The lymph nodes, spleen and liver are usually involved. The nodes and spleen may show an absolute increase in both size and number of germinal follicles. The characteristic cell is the adult lymphocyte, many of which are undergoing active mitosis. The follicular enlargement is evident in both the cortical and medullary areas (3).

Follicular lymphosarcoma.—Here the lymphocyte may be slightly larger than the usual small lymphocyte. These lymphocytes stain deeply, are actively mitotic and break through the follicles with diffusion through the node or spleen (3).

Lymphosarcoma (diffuse).—This is the classic form. It is manifested by the presence in node, spleen, liver or other viscera of deeply staining abnormal lymphocytes with high mitotic activity diffusing throughout the tissue involved, as well as the areolar and fatty tissue, such as perinodal fat. The cells may be small and mature looking (lymphocytoma or lymphocytic lymphosarcoma) or large (lymphoblastic lymphosarcoma) (4).

Reticulum Cell Sarcoma

Nodal, splenic, hepatic or other visceral involvement is common. The diagnostic microscopic picture is that of replacement of the invaded tissue by increased numbers of reticulum cells and reticular fibrils. The reticulum cells are larger and more pleomorphic than lymphocytes (4).

As in the case of Hodgkin's disease, biopsies of different nodes in the same patient may reveal any or all of the varieties of lymphosarcoma, and occasionally, examination of numerous sections of a single lymph node may demonstrate all the types.

As important as the histologic diagnosis of the patient with malignant lymphoma is the clinical classification of such a patient at the time of initial examination. A clinical classification is imperative to determine whether the patient shall have either curative or palliative therapy, and, subsequently, an ex-

cellent, good or poor prognosis. This type of classification is significant also in that it selects or modifies not only the type of therapeutic modality, but the dosage and vigor of the treatment. The clinical classification which follows relates to Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma:

CLASS I.—Disease limited clinically to a single locus (unifocal, unicentric origin); no constitutional symptoms or signs (i.e., fever, night sweats, pruritus, weight loss, anemia, fatigue).

CLASS II.—Disease limited regionally (regional anatomic distribution, i.e., all apparent disease above the diaphragm, or all apparent disease below the diaphragm) with or without constitutional symptoms and signs.

CLASS III.—Generalized (universal disease with constitutional symptoms and signs) (4).

CLINICOPATHOLOGY

Jackson and Parker (2) are the main protagonists of the thesis that the patient with Hodgkin's paragranuloma has the most benign *clinical* course. Others (6, 7, 8, 9) indicate that irrespective of the histologic type, the paramount factor is the *clinical* class into which the patient falls when he is *first* seen, *diagnosed* and *adequately* treated. This is true also of the patient with lymphosarcoma and reticulum cell sarcoma (4). An investigation presently in process bears out this contention (10). It cannot be stressed too strongly that a dynamic approach to both diagnosis and treatment must be taken and that the clinician should not wait for the appearance of symptoms as a criterion for beginning treatment. The sooner the recognition of the presence of beginning and localized malignant lymphoma and the earlier the institution of therapy the better, usually, will be the prognosis (6, 7, 8, 9).

NATURAL HISTORY AND TREATMENT

There are three main categories of treatment for Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma. They are surgery, radiation therapy and chemotherapy.

SURGERY

Surgical therapy of the malignant lymphomas should be reserved for selected and special clinical situations. At the Me-

morial Center for Cancer and Allied Diseases, consideration for surgical treatment is given to patients in only the clinical Class I category. Even then, further selection must be exercised and those patients chosen who demonstrate disease only in the upper part of the neck, the lower segment of the axilla or the femoral fossa, when the disease is nodal. When the disease is extranodal and primary in the stomach, small intestine, large intestine, kidney, ovary, testicle, lung, pancreas, spleen, urinary bladder, prostate gland, vagina or uterus, surgical therapy is chosen. When surgery is elected as the treatment of a *primary* malignant lymphoma, en bloc radical cancer surgery must be performed. Examples of such procedures would be radical axillary, groin or neck dissection; subtotal or total gastrectomy; and radical pneumonectomy. After the radical surgical extirpation of either thoracic or abdominal structures, if the regional lymph nodes are found on microscopic section examination to be positive for malignant lymphoma, x-ray therapy should be given postoperatively to the patient. It is our belief that postoperative x-ray therapy in moderate dosage should be given also in any peripheral area where radical dissection has been performed.

Whereas, at least theoretically, the foregoing reasons for surgery have been reviewed with cure in mind, on occasion palliative surgical measures are indicated as well. Such instances are, to cite a few, large or recurrent bleeding lymphomatous ulcer of the stomach or bowel, intestinal obstruction due to recurrent intraluminal lymphomatous tumor or to recurrent x-ray-resistant large retroperitoneal nodes, or when, as sometimes happens, the bulk of the tumefaction in an area is so great as to make well-conceived and well-planned x-ray treatment impossible. In all instances where palliative surgery is used in patients with malignant lymphomas, the procedure should be carefully planned, expertly executed, definitive, and yet as conservative as possible. The operation should be done by a surgeon with experience in the vagaries, both clinical and surgical, of these diseases.

Radiation Therapy

X-ray therapy has been a favored and effective form of therapy in the United States for the treatment of malignant lymphomas and leukemias since the beginning of the twentieth

century (11, 12). It remains the most beneficial type of treatment of these diseases to date. Radioactive phosphorus has little usefulness in the management of malignant lymphomas (13). For the patient in clinical Class I, obliterative x-ray therapy should be given with cure as at least the theoretical aim. X-rays generated in the range of 250 to 1,000 kv. should be used. A total dose of 3,000 to 3,600 r in air in 2-3 weeks

CLASSIFICATION OF X-RAY VOLTAGES

Contact	To 60 kv.
Low voltage	35-125 kv.
Medium voltage	130-198 kv.
High voltage	200-800 kv.
Super voltage	1,000-3,000 kv.
Mega voltage	23 Mev (betatron)

through sufficient portals to encompass the areas of disease should be delivered. Similarly, to the patient with clinical Class II disease when no constitutional symptoms exist, using similar voltages, moderately aggressive doses in the order of 2,000 to 2,400 r in air in 2-3 weeks should be delivered to portals encompassing the areas of disease. If the patient tolerates the therapy well and the portals are not too large, 2 treatments daily to paired portals may be given in order to shorten the over-all treatment period. When constitutional symptoms and signs exist, the patient should receive a full course of nitrogen mustard before the prescribed course of x-ray therapy. These patients are treated in the fashion described, with long-term palliation as the prime consideration.

Finally, for patients with clinical Class III disease, simple palliation is the aim of treatment. Therapy should be administered by high voltage x-ray generators to areas of disease which by virtue of size, bulk or position are causing distressing symptoms, or which by location in juxtaposition to certain structures are causing obstruction or compression of vital organs. Only enough irradiation should be given to cause sufficient shrinkage of the tumor mass to alleviate symptoms. When it seems advisable to ameliorate constitutional symptoms quickly, nitrogen mustard (HN2) may be given before x-ray therapy.

The most significant rule to remember in treating patients

with clinical Class III disease with x-rays is that the patient is the restricting factor of the amount of x-ray therapy tolerated, and not the tumor, remembering always that it is a patient and not just a cancer that is being treated.

Chemotherapy

The discipline of cancer chemotherapy has become established firmly in the past decade. It has been in the management of malignant lymphomas and leukemias that such agents have been demonstrated to have a salutary effect. The aliphatic nitrogen mustard, methyldi-2-chloroethylamine (HN2), and the polyethylenimine, triethylene melamine (TEM) are two significant chemotherapeutic agents. In addition, the adrenal steroidal hormones, cortisone, hydrocortisone, prednisone and prednisolone, and the adrenal corticotropic hormone (ACTH), have demonstrated provocative effects in patients with malignant lymphomas.

HN2 (methyldi-2-chloroethylamine).—This compound is a general cell poison which is cytotoxic, especially to lymphoid tissue and bone marrow (14, 15). The modification it produces on tumor cells is indistinguishable microscopically from that of ionizing radiations (16). For this reason it is called a radiomimetic agent. It provides an adjunctive method of treatment for patients with Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma who have disseminated disease and constitutional symptoms. HN2 affords a means of rapid detoxification of such patients.

It is our practice to use HN2 alone or, more frequently, in conjunction with x-ray therapy in patients with clinical Class II or Class III disease. We find this compound and its congeners most important when constitutional symptoms are the singular problem. Although the average remission with HN2 may last only 1-2 months, many patients have remained well for longer periods. Numerous repeated courses of HN2 may be given after sufficient time has elapsed for the blood and bone marrow to recover. This material causes lympholysis and leukopenia (especially lymphopenia) and thrombocytopenia. In toxic doses it can destroy the bone marrow. Successive courses of treatment with HN2 usually result in less satisfactory remissions in terms of degree of response and duration.

The total course of HN2 usually amounts to 0.4 mg./kg. of body weight intravenously. The dose may be fractionated so

that 0.1 mg./kg. of body weight is given intravenously daily for 4 successive days (0.1 mg./kg.×4), 0.2 mg./kg. daily intravenously for 2 successive days (0.2 mg./kg.×2) or as a single dose intravenously of 0.4 mg./kg. (0.4 mg./kg.×1). The amorphous white powder, HN2, is placed into solution freshly with sterile isotonic saline solution so that 1 mg. of drug is contained in 1 cc. of diluent. In order to mitigate the thrombophlebitic tendency of HN2, the compound is then injected through the tubing of a 250 cc. infusion of sterile isotonic saline solution which is actively running into a vein. When this maneuver has been completed, the remaining infusion is allowed to run into the vein quickly for its dilution and flushing effect. HN2 causes nausea and vomiting in up to 80% of patients. For this reason, we prefer to give the material in a single dose of 0.4 mg./kg. whenever possible, since the period of nausea and vomiting is then not protracted over several days, as it is with the fractionated method. Antinauseant drugs should be administered, but always *after* the HN2 has been given, *not before*. It is wise to wait for one-half hour after HN2 has been given to the patient before administering such agents as pyridoxine or chlorpromazine or their analogues, so that there is little chance, if any, of cross-reactivity of the HN2 with these agents prior to the fixation of the HN2 in the tissues.

A complete hemogram of the patient should be made, including a platelet count, before HN2 is administered. Whenever possible, a pretreatment bone marrow aspiration should also be performed. When the white blood cell count and platelet level are normal, 0.4 mg./kg. of HN2 may be given. When the bone marrow is normocellular or hypercellular and megakaryocytic activity is normal, this dose may be given safely despite a mild peripheral leukopenia. When there is moderate leukopenia and thrombocytopenia and the bone marrow is hypocellular, HN2 should be reserved for desperate clinical situations.

HN2 is highly toxic to all cells, but more so to those of the bone marrow, lymph nodes and reticuloendothelial system. Consequently, it is effective in diminishing the size of enlarged lymphomatous nodes, spleens and livers. Fever often is abated within 24-48 hours. Appetite may become voracious after nausea has subsided. Well-being is achieved frequently, as is weight gain. Leukopenia occurs anywhere from the 6th to the 21st day after injection of the drug. Bone marrow and blood

recovery is usually complete within 6 weeks after the compound has been given. All patients must be followed with frequent post-treatment blood counts, including platelet counts, until normal or near-normal levels have ensued.

TEM (TRIETHYLENE MELAMINE).—This compound has pharmacologic and toxicologic properties quite similar to HN2 (17, 18, 19, 20). It, too, is a radiomimetic agent. In contrast to HN2, it is effective when taken orally. Its ethylenimine portion is similar chemically to the ethylimmonium linkage of HN2. It is effective in the treatment of Hodgkin's disease, somewhat less so in lymphosarcoma and least effective in reticulum cell sarcoma in the group of malignant lymphomas. Lymphosarcoma cells are exquisitely sensitive to this agent, and small, cautiously administered doses are indicated in the treatment of this disease with this agent. Patients are treated on an ambulatory basis. The indications for the employment of TEM are the same as those for HN2.

We use the drug in the form of a white scored 5 mg. tablet. It should be stored in a refrigerator. Six months after its production date the drug loses its potency and should be discarded. For patients with Hodgkin's disease and reticulum cell sarcoma who have been first shown to have adequate white blood cell and platelet counts and active bone marrow the usual course is 10 mg. in 1 week, repeated the following week or after a lapse of 1 week, not to exceed 30-40 mg. in any month. The dose is fractionated so that 2.5 mg. (½ tablet) is taken on an empty stomach with water only, ½ hour before breakfast daily for 4 days. The incidence of nausea and vomiting is considerably less after TEM than after HN2 (17, 18, 19, 20). Again, as with HN2, patients given TEM must have frequent blood counts performed. Bone marrow recovery as well as an upsurge of leukocyte level becomes apparent usually in 4-6 weeks after the administration of the first dose of the agent. TEM can be given intravenously as a dose of 0.04 mg./kg., ×3 (0.12 mg./kg.) with the total course usually consisting of 6-9 mg.

Patients with lymphosarcoma are uniquely sensitive to TEM. Profound rapid leukopenia and thrombocytopenia may be induced. For this reason, it is advisable that no more than 2.5-5 mg. (2.5 mg. × 2) by mouth of this agent be administered to such patients in any week. Usually it is then prudent to wait 1 week, checking the blood count frequently, before embarking on another course of TEM. As a result of the rapid break-

down of the tumor tissue following TEM, hyperuricemia may ensue, leading to hyperuricuria and even renal shutdown (3, 17). This problem is best treated by prevention, if possible, and the clinician must be alert to the possibility of this complication arising. Treatment consists of alkalinization (since uric acid is 30 times more soluble in alkaline urine than acid urine) and forced fluid intake either orally or intravenously to allow for diuresis. If this measure fails, then cystoscopic retrograde catheterization of the renal tract and flushing out of the renal pelves, ureters, bladder and urethra with isotonic sterile saline solution or sterile sodium bicarbonate solution are indicated (17).

Enlarged lymph nodes, livers and spleens will usually shrink in size after TEM therapy. Pruritus often abates. Fever frequently disappears promptly. Remissions, though usually short-lived, may last for several months. Maintenance therapy can be attempted. Recently, chlorambucil (CB 1348) has been introduced and has the same indications and usefulness as TEM (21, 22). We believe that this newer agent has shown no improved results over those of TEM and HN2. It is merely another radiomimetic agent added to the chemotherapeutic armamentarium useful in the treatment of the malignant lymphomas. This statement is likewise similarly applicable to other experimental agents such as Myleran®, Actinomycin C and D and the hemisulfur mustards.

HORMONES.—The adrenal steroidal hormones, cortisone, hydrocortisone, prednisone and prednisolone and the adrenal corticotropic hormone (ACTH) have several provocative effects on patients with malignant lymphomas. First, a specific effect, that of lympholysis; second, nonspecific manifestations, namely, reduction of fever, improvement of appetite and increased sense of well-being. These compounds may be used as an interval form of therapy in patients with clinical Class II disease and as a sustaining mode of therapy for clinical Class III patients.

These materials have no specific antitumor effect on Hodgkin's disease, but do on lymphosarcoma and reticulum cell sarcoma. When acquired hemolytic anemia supervenes, as it does from time to time in patients with malignant lymphomas, these agents may produce an improvement. The usual toxic manifestations of these hormones are well known. Some of the more disturbing ones are the genesis of peptic ulceration with or without bleeding or perforation and consequent peritonitis,

often clinically silent; massive monilial infection, bacterial septicemias and spontaneous lung abscess formation (23). Once committed to this form of therapy it is often difficult to withdraw these agents from the patients. Because of the serious side-effects noted above, the physician always must be on the alert, and impeccable in his care of the patient.

The dosage range in patients with malignant lymphomas is moderate to high, and, under experimental circumstances, even as much as 1 Gm. per day of prednisone has been used. The usual dose for cortisone is from 100 to 300 mg. per day orally in divided doses; for hydrocortisone, approximately ⅔ of this amount; for prednisone and prednisolone 20-60 mg. per day orally in divided doses. ACTH may be given intravenously as 40 mg. in a liter of 5% glucose in sterile water; intramuscularly as 40-200 mg. in divided doses, or as a gel or zinc suspension 40-80 units (occasionally up to 120 units) once daily intramuscularly. Recently, in desperate clinical situations, as much as 1 mg. of prednisone in divided doses over a 24-hour period has been administered to patients with malignant lymphomas, with some salutary but unpredictable effect.

The natural history of the malignant lymphomas is best shown by a review of the various body systems which become involved, and the pathophysiologic alterations which ensue therefrom. The appropriate methods of management will be reviewed. The magnitude and dynamicism of these diseases can be appreciated fully when it is realized that they can occur in any tissue or organ system of the body.

INTEGUMENT AND DERIVATIVES

Hodgkin's disease of the skin is a rare phenomenon. It may be nodular and circumscribed, or infiltrative, diffuse or ulcerative. Brownish pigmentation of the skin is not uncommon even in patients who neither have itching nor have received x-ray therapy. Numerous varieties of dermatoses, usually nonspecific, are associated with Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma. These are eczematoid reactions, exfoliative dermatitides and toxic erythemas. Herpes zoster occurs in many patients with Hodgkin's disease sometime during the course of their disease. Excoriative dermatitis brought on by the patient's scratching of pruritic areas of the skin is quite common.

Lymphosarcoma and reticulum cell sarcoma commonly in-

volve the skin. They may appear as cutaneous or subcutaneous circumscribed, ulcerative colorless or violaceous lesions of varied size, most frequently in the scalp.

The breast may be a site of either Hodgkin's disease, lymphosarcoma or reticulum cell sarcoma. Frequently, the mass or masses present in the breast are indistinguishable clinically from carcinoma (24).

Treatment is accomplished best by local x-ray therapy to the skin lesions with low or high voltage generators depending on the "iceberg" quality of the skin tumors. When the lymphomatous process is extremely widespread in the skin, chemotherapy with the polyfunctional alkylating compounds is useful. The nonspecific dermatoses are treated best by controlling the underlying lymphoma as efficiently as feasible, with local emollients and with adrenal steroidal hormones and ACTH.

Solitary breast lesions may be excised, but more often are treated with x-rays. For multiple lesions of the breast x-rays are undeniably the best treatment.

SOFT PARTS OF THE HEAD AND NECK

Ulcerative or polypoid lesions of the nasal and paranasal sinuses due to malignant lymphomas occur. Retro-orbital and orbital involvement is not uncommon (25). The tonsils and nasopharynx, especially in lymphosarcoma and reticulum cell sarcoma, frequently are loci of disease. The tongue and thyroid gland are occasionally foci of malignant lymphoma. Extraocular muscle palsies are due most often to lesions localized at the base of the brain in the posterior fossa (26).

The most effective form of treatment of head and neck lymphomatous disease is x-ray therapy, carefully planned and administered, and with the employment when necessary of special radiation technics. When there is tracheal invasion, compression or obstruction and airway compromise, it is wise to use HN2 *before* x-ray therapy to avoid the possibility of further compression by expansion-swelling of the tumor mass as an immediate response to the x-rays.

THORAX

Mediastinal adenopathy is a common manifestation of the malignant lymphomas (27). Obstruction of the trachea or

bronchi may result in cough, dyspnea and substernal pain. Atelectasis and even suppuration distal to the point of bronchial obstruction may result. Endobronchial polypoid and ulcerative lesions due to malignant lymphomas have been observed and biopsied through the bronchoscope.

The pleura may be thickened considerably by the malignant lymphomas, and pleural effusions are relatively common when the pleura is involved with these diseases. In such settings, the effusion is an exudate and may be frankly sanguineous. Pleural effusion due to great-vessel compression by mediastinal tumefaction is a fairly common event in the lymphomas and is differentiated from that due to pleural or pulmonary invasion by virtue of the fact that the fluid is transudative and due to increased hydrostatic pressure in the great veins. Superior vena caval compression syndrome may occur. Chylous effusion due to compression obstruction of the thoracic duct happens occasionally. In carcinoma, the thoracic duct is almost always invaded, in contradistinction to compression only by the lymphomas, when chylothorax exists.

There is no characteristic roentgen pattern associated with pulmonary invasion by the malignant lymphomas. The lesions may appear solitary or multiple, nodular or infiltrative, diffuse, lymphangitic or miliary. Bronchopleural or tracheoesophageal fistulae may ensue. Lung cavitation is seen rarely, but more often in Hodgkin's disease than in lymphosarcoma or reticulum cell sarcoma (27).

In addition to the usual measures used to combat bronchospasm, pulmonary suppuration, bronchial and pulmonary bleeding, pleural effusion and atelectasis, remedial definitive x-ray therapy to the locus of the disease is a frequently effective method of treatment. HN2 is indicated before x-ray therapy in the management of the superior vena caval compression syndrome to mitigate the possibility of further compression and obstruction due to the swelling of the tumor mass following the initiation of the x-ray therapy, as well as for its own salutary antitumor effect.

The heart is involved by these diseases and the leukemias more often than by any other cancer except malignant melanoma (28, 29). The myocardium, the pericardium and, rarely, the valvular structures, may be affected by these tumors. Pericardial effusion, conduction abnormalities, bizarre cardiac rhythms not corrected by cardiotonic drugs and congestive failure may be noted. In addition to the usually employed

remedial measures for the treatment of pericardial effusion and myocardial disease of any type, definitive treatment with x-rays and occasionally by combination therapy with HN2 may afford considerable to complete alleviation of symptoms and signs due to lymphomatous disease at these sites.

GASTROINTESTINAL TRACT

Primary lesions occur occasionally and secondary invasion of the digestive tract is more common. These tumors may arise anywhere from mouth to anus.

In the esophagus the tumor may be submucosal, break through the mucosa, ulcerate and bleed. Primary malignant lymphomas of the stomach make up perhaps 5% of all gastric malignant tumors. They are mass lesions or ulceropolypoid in type. In the small intestine they are at least as common as adenocarcinomas. The appendix and large intestine are not infrequently the locus of invasion by polypoid, ulcerative or obstructive tumors of malignant lymphomatous disease.

Treatment may have to be surgical if the intragastric tumor or bowel tumor is large and ulcerative. Surgery is needed less often for obstructive lesions. X-ray therapy is the treatment of choice for obstructive lesions as an initial form of definitive treatment. Gastric and bowel lymphomatous tumors causing small ulcerations or minimal bleeding should be treated first with x-rays; however, if bleeding does not cease promptly during or immediately after a course of such therapy, surgery should then be done. Primary malignant lymphomas of the stomach and bowel should be resected surgically, and if positive nodes are found, postoperative radiation therapy given. Chemotherapy with the cytotoxic agents is almost futile when bulky or ulcerating gastrointestinal lesions are present.

GENITOURINARY SYSTEM

The kidneys may be enlarged by tumor invasion secondary to retroperitoneal or para-aortic nodal disease. Primary involvement is rare. Obstruction to urinary outflow, hemorrhage or cessation of urine formation may occur. Ureters are frequently displaced by para-aortic and retroperitoneal lymphomatous deposits. The bladder and prostate may become secondarily involved from juxtapositional nodal disease. Oc-

casional primary prostatic involvement may ensue (30). The ovaries and testes may be invaded, more frequently by reticulum cell sarcoma and lymphosarcoma than by Hodgkin's disease. Tumors at these sites are usually nodular, but they may become ulcerative.

X-ray therapy of the renal tract to include the kidney, ureter and bladder may be necessary at times. Isolated lesions of the vulva, testicle, vagina, prostate and the ovaries may be treated easily with x-rays. Ovarian lymphomas and testicular lymphomas may also be treated with some degree of beneficial effect with the polyfunctional alkylating compounds.

SKELETAL SYSTEM

Primary reticulum cell sarcoma of bone has been described and considered by some to be a primary bone tumor (2, 31, 32). We believe that this disease is merely another form of primary origin of malignant lymphoma (clinical Class I). Lymphomatous involvement of bone is quite common. In Hodgkin's disease the lesions are often a mixture of lytic and blastic components, whereas in lymphosarcoma and reticulum cell sarcoma the lesions are more purely lytic in character. Any area of the skeleton may be attacked. Sometimes pain in a bone may precede observable roentgen change due to tumor by several months. Occasionally, hypercalcemia and hypercalciuria may indicate just such an event before the observation of any obvious roentgen abnormality. Pathologic fractures occur occasionally.

Conservative orthopedic measures followed by x-ray therapy to the areas of fracture are indicated when pathologic fractures occur. X-ray therapy to areas of bone involvement may produce satisfactory results as measured both by pain relief and roentgenologic appearance. The biochemical abnormalities of calcium metabolism may be altered in the direction of normal by radiation therapy.

NERVOUS SYSTEM

Spinal cord compression by lymphomatous tumor occurs occasionally with resulting paraplegia. The usual mechanism for this complication is not vertebral body collapse from tumor in the vertebral body and then transverse myelitis, but rather

epidural invasion and extension and compression by growth through the intervertebral foramina and then circumferential and linear extension in the epidural space, the extension originating from para-aortic, mediastinal or retroperitoneal nodal lymphomatous disease (3, 26). Immediate recognition of this problem is vital if treatment is to be successful; and successful it can be at least 50% of the time if the disease is treated early with a combination of HN2 and then a full course of x-ray therapy to the appropriate neurologic level of the cord. The brain may be compressed by a dural lymphomatous tumor. Again, early recognition of this possibility, careful neurologic examinations and localization and vigorous treatment with combination chemotherapy and radiation therapy will often result in satisfactory amelioration. Torulosis, a nefarious complication, occurs in a significant number of patients with malignant lymphomas and usually manifests itself by the signs of a smoldering meningitis. The organism Cryptococcus neoformans may also involve the skin, bones and reticuloendothelial system. Unfortunately, no specific treatment is known to be successful for this dreaded complication.

BLOOD AND BONE MARROW

The leukocyte count encountered frequently in the malignant lymphomas is somewhat elevated, with a shift to the left characterized by polymorphonucleosis. In lymphosarcoma patients a lymphocytic predominance in the differential blood count bodes a change to chronic lymphatic leukemia (lympholeukosarcoma). Following x-ray therapy, and even more dramatically after giving the polyfunctional alkylating chemotherapeutic compounds, leukopenia and especially lymphopenia become apparent. A rare phenomenon indeed is the presence in the blood of a morphologically aberrant cell type which unequivocally can be called a lymphosarcoma cell.

The problems of anemia in the malignant lymphomas are many. Anemia occurs as a natural event in the course of these diseases in perhaps 15-20% of the cases. This result is produced occasionally by the use as therapeutic modalities of bone-marrow-depressing agents such as x-rays and the nitrogen mustards and their congeners. These forms of therapy are to a relative degree myelosuppressive. The anemia may be due to blood loss from gastrointestinal or genitourinary tract lesions. It is,

in the main, normochromic, unassociated with known blood loss, but only with activity and progression of the malignant lymphomatous process. Recent studies of the life span of the red blood cells of patients with malignant lymphomas have revealed a shortened life span (33, 34). Thus another explanation of one of the mechanisms for anemias in these patients has become known. Acquired hemolytic anemia may supervene; this happens somewhat more often in lymphosarcoma patients and chronic lymphatic leukemic patients than in patients with Hodgkin's disease or reticulum cell sarcoma. Only infrequently can a true erythroleukoblastic state (myelophthisis) be demonstrated to exist clinically.

The best approach to the treatment of the anemias of the malignant lymphomas is the treatment of the underlying tumorous condition itself; suppressive therapy of the malignant lymphoma will usually ameliorate to varying degrees the severity of the anemia. Transfusions of packed red blood cells are necessary at times to tide the patient over until the anemia abates, or fairly permanently, as the only specific measure in some patients. The acquired hemolytic anemias may be altered by the employment of adrenal cortical hormones or ACTH. Such treatment may have to be continued for several months before considering it fully successful or a failure. X-ray therapy to the splenic area may cause abatement of the anemia due to the hemolytic state.

Thrombocytopenia becomes a problem both as a complication of the natural course of the disease and as a consequence of the use of myelosuppressive agents, either x-rays or chemotherapeutic antimitotics. Occasionally, effective treatment of the underlying malignant lymphoma effects a return of the platelet level to normal range. Bleeding, as evidenced by petechiae, ecchymoses, purpura, epistaxis, occult blood in the feces, microscopic hematuria and gum bleeding are often associated with the thrombocytopenic state in these patients. On occasion, the bleeding phenomena mentioned occur in the face of normal platelet levels. There is accumulating evidence to suggest the presence of relative hypofibrinogenemic states in some of the patients with malignant lymphomas and leukemias, and fibrinolysins in others of this category of patients (35, 36).

There are no characteristic bone marrow findings in Hodgkin's disease. Rarely, indeed, can a Sternberg-Reed cell be identified unequivocally in a marrow aspiration specimen.

Occasionally these cells can be recognized on formal bone marrow sections. The diagnosis of Hodgkin's disease of the marrow depends not only on the presence of Sternberg-Reed cells, but also on being able to identify necrosis, fibrosis and eosinophilia as well. There is often normocellularity as concerns the white blood cells, and variations of erythrocytic and megakaryocytic activity, depending on the status of activity of the malignant lymphoma (clinical Classes I, II or III), whether treatment has been given previously, whether it has been chemotherapy or x-ray therapy and, finally, whether marrow-producing bone has been directly in the path of previously given therapeutic ionizing radiations.

LIVER AND PANCREAS

Involvement of the liver by the malignant lymphomas is not at all uncommon late in the course of these diseases. Rarely, a fulminating miliary involvement of the liver may occur in that form of Hodgkin's disease known as miliary Hodgkin's disease, an extremely acute variety. Hyperbilirubinemia, when present, may be due to hemolysis, but most often is the result of hepatic infiltration by one of the malignant lymphomas. Elevations of serum enzymes such as transaminases may be helpful in demonstrating liver involvement by the tumor (37). In the nonicteric patient the combination of elevated bromsulphalein retention and elevated alkaline phosphatase (when no evidence of bone disease exists) is significant as a most reliable sign of hepatic involvement by lymphomatous tumor (38). The supervention of viral hepatitis in these patients must be kept in mind constantly. Chlorpromazine hepatitis may occur in those patients receiving this drug as an antinauseant, and a methyltestosterone hepatitis may occur in any patient receiving that hormone.

Lymphomatous liver disease may be treated with some success by the use of therapeutic x-rays to the liver; less successful but still worth using are the nitrogen mustards and other alkylating compounds. Correction of any excessive hemolytic state causing hyperbilirubinemia must always be attempted. Cessation of the administration of methyltestosterone and chlorpromazine should allow for spontaneous healing of a liver so affected.

The pancreas may be a site of lymphomatous disease, almost always not primarily. Exocrine function is not ordinarily al-

tered. Many patients with malignant lymphomas when screened with glucose tolerance studies show diabetic curves (39); whether this correlates with actual pancreatic invasion has not yet been determined. The pancreatic area is indeed treatable with fair success with x-rays.

Extrahepatic biliary obstruction by malignant lymphomatous nodes at the porta hepatis may occur. Such a clinical setting is amenable to x-ray therapy delivered to the porta hepatis, with frequent relief of the obstructive symptoms and signs.

END RESULTS OF TREATMENT

End results of treatment in Hodgkin's disease vary with the clinical stage of the disease. Peters (6), treating patients mostly in clinical Class I, recorded a 5-year survival rate in excess of 50%. For patients in all the clinical classes (Classes I, II and III) a 25% 5-year survival rate is reported (3). Catlin reported a 52% 5-year survival rate in patients with clinical Class I lymphosarcoma and reticulum cell sarcoma of the head and neck area treated with x-rays (1). Coley (31) has reported a 52% 5-year survival rate for patients he characterizes as having primary reticulum cell sarcoma of bone. These patients were treated with x-ray therapy.

What is most salient is that treatment prolongs the patient's *comfort* if not actually his life. An aggressive, dynamic approach to the patient with malignant lymphoma is required if his life is to be prolonged. Careful and frequent clinical examinations coupled with dynamic therapy can only improve the results of our treatment and the gratitude of our patients.

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